

REMARKS/ARGUMENTS

Claims 1, 2 and 8 are pending in this application and remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bottger *et al.*, 1996 (Oncogene, 13:2141-2147), in view of McCann A H *et al.*, 1995 (British J Cancer, 71(5):981-5), and further in view of Lee JM, 1995 (Cancer and Metastasis Review, 14(2):149-161) “for reasons already of record in paper of 07/18/06.” (Advisory Action, page 2).

The Examiner has not been convinced by Applicants’ arguments submitted in response to the rejection first raised in the Final Office Action of July 18, 2006, essentially for the following reasons:

1. There is no evidence that McCann *et al.* teach that mdm2+ status (type 2) indicates overexpression of mdm2. The Examiner notes that it is “not clear what facts that Applicant interprets as overexpression, when only 10 to 50% of cells are detected with mdm2 protein.” (Advisory Action, page 3, second full paragraph, emphasis omitted).

2. From the data taught by McCann *et al.* “it is clear that in table III, on page 983, the presence of mdm2 protein is correlated with low level of p53, even for breast cancer type 1 in which only less than 10% of cells express mdm2 protein.” (Advisory Action, page 3, third full paragraph, emphasis omitted). Based on the data presented in Table III, the Examiner concludes that “from the teaching of McCann *et al.*, one would conclude that in breast cancer cells, the presence of mdm2, even at less than 10% of cancer cells, or between 10-50% of cancer cells, is significantly associated with low level of p53.” (Advisory Action, page 4, lines 1-4).

3. From the teaching of McCann *et al.*, “it is clear that there is no correlation between mdm2 gene copy number and level of mdm2 protein.” (Table II on page 983).” (Advisory Action, page 4, first full paragraph). Accordingly, based on this teaching, “one cannot predict that increased mdm2 protein level is found in mdm2 type 2 breast cancer having no alteration of mdm2 copy number,” or that increased mdm2 mRNA level in patients with no alteration in mdm2 copy number (Buesco-Ramos *et al.*, 1993 and Sheikg *et al.*, 1993), would indicate increased mdm2 protein level in breast cancer patients with no alteration in copy number. (Advisory Action, page 4, first full paragraph).

4. In addressing Applicants’ argument that there is nothing in McCann *et al.* to suggest that targeting of the mdm2/p53 may be of use when mdm2 is not over-expressed, the

Examiner states that the cited references provide motivation for using a peptide inhibitor of mdm2 and p53 interaction, for treating those cancer cells that do not overexpress mdm2, “because in these cancer cells, the level of p53 is low, and is associated with the expression of mdm2, as taught by McCann *et al.*” (Advisory Action, page 5, first paragraph).

In conclusion, the Examiner notes that the obviousness rejection stands since: (1) loss of p53 function is correlated with increased resistance to chemotherapeutic agents (Lee *et al.*); (2) hdm2 binding to p53 has been known to inactivate p53 function, and it is thus desirable to design peptides that interfere with the mdm2-p53 interaction to restore p53 function (Bottger *et al.*), and (3) in cancer cells which do not overexpress mdm2, the presence of mdm2 is significantly associated with low level of p53 (McCann *et al.*). (Advisory Action, page 5).

Applicant disagrees and vigorously traverses the rejection.

The References

Bottger *et al.* teaches that the oncogene Mdm2, and its human homologue hdm2, bind to the tumor suppressor protein p53 and inactivates its function as a positive transcription factor. The Examiner has relied on Bottger *et al.* because it discloses a peptide (clone 12/1), which is shown to interfere with binding between hdm2 and p53, and that Bottger *et al.* conclude that “Using these new and high affinity inhibitors will now allow experiments to provide proof of principle for the biological significance of the concept that challenging the p53-hmd2 interaction is a possible route for anti-cancer treatment.”

McCann *et al.* discloses studies into the frequency of Mdm2 over-expression in breast cancers. They look at both gene amplification and protein expression and find that only 7% of these cancers show over-expressed Mdm2. The conclusion from these studies is that inactivation of p53 as a consequence of Mdm2 over-expression occurs in only few breast cancers. As stated by McCann *et al.*, “We conclude that MDM2 gene amplification occurs at a lower frequency in breast cancer than in non-epithelial tumours.” (Summary, lines 8-9). McCann *et al.* also examine p53 expression. They show that, as expected, over-expression of Mdm2 is associated with low levels of p53. It is important to realize that low p53 levels are indicative of the retention of wild-type p53 – so this supports the view in the art that over-expression of Mdm2 can inhibit p53. However, the study suggests that this correlation is not complete, and in some cancers alterations in both Mdm2 and p53 may have occurred.

The study by McCann *et al.* shows that although most breast cancers do not over-express Mdm2, a few of them do show elevated Mdm2 expression, and these tumors are significantly associated with low (*i.e.*, wild-type) p53 levels. McCann *et al.* state that “*at the protein level, MDM2+ tumours were significantly associated with tumours having low levels of p53 staining.*” (Summary, lines 7-8). This means that those few breast cancers that over-express Mdm2 tend to show low levels of p53 – indicating a retention of wild-type p53.

Lee *et al.* has been relied on for allegedly teaching that “p53 could induce apoptosis and cell cycle arrest, and that low of p53 function causes increased resistance to chemotherapeutic agents.”

As discussed above, the Examiner is of the opinion that it would have been obvious to use the peptide of Bottger *et al.* to disrupt binding of p53 and Mdm2 in tumor cells, to increase the activity of p53; and that it would have been obvious to target any cancer cells that express p53 and Mdm2, including those populations of cancer cells that do not over-express Mdm2, such as breast cancer cells taught by McCann *et al.*, because loss of p53 function is correlated with increased resistance to chemotherapeutic agents, as taught by Lee *et al.*

The cited combination of references does not make obvious the claimed invention

Presented below, and supported by a Declaration of Professor Karen Vousden, are reasoned arguments showing that the claims pending in the subject application are unobvious over the cited art and the common general knowledge in the art at the time the present invention was made.

The Examiner is reminded that to reach a proper determination under 35 U.S.C. §103, the Examiner must step backward in the time and into the shoes worn by the hypothetical “person of ordinary skill in the art” when the invention was unknown and just before it was made. In view of all factual information, the Examiner must then make a determination whether the claimed invention “as a whole” would have been obvious at that time to that person. Knowledge of Applicants’ disclosure must be put aside in making this determination, yet kept in mind in order to determine the “differences,” between the claimed invention and the state of the art, conduct research and evaluate the “subject matter as a whole” of the invention.

The present application was filed on April 20, 1998 as PCT/GB98/01144. It claims priority from GB9708092.3 filed on April 22, 1997. The pending claims are all supported by the

disclosure in the priority application and consequently the date at which the “state of the art” is to be considered is April 22, 1997. Applicants submit that one of ordinary skill in the art at the relevant time would not have combined the teaching of the cited references and certainly would not have done so with a reasonable expectation of success.

As supported by the enclosed Declaration of Professor Karen Vousden (one of above ordinary skill in the art), it was understood at the priority date of the present application that inhibition of p53 function is important for the development of many cancers. It was also understood that this might be the consequence of a number of different events such as (but not limited to).

1. Mutation within the p53 gene.
2. Over-expression of Mdm3 – a known negative regulator of p53.
3. Expression of the human papilloma virus E6 protein.

There was evidence that these alterations are mostly mutually exclusive. In other words, tumors with E6 or Mdm2 over-expression do not have mutated p53 and *vice versa*. The understanding was that it is only necessary to inactivate p53 through one mechanism. (Crook *et al.*, *Oncogene* 6:873-875, 1991; Scheffner *et al.* *PNAS* 88:5523-5527, 1991; Crook *et al.*, *Lancet* 339:1070-1073, 1992; Leach *et al.*, *Cancer Res.* 53:2231-2234, 1993; Oliner *et al.*, *Nature* 358:80-83, 1992 – copies enclosed with an attached Information Disclosure Statement). Two papers were published in 1995 (Jones *et al.*, *Nature* 378:206-208, 1995; and Montes de Oca Luna *et al.*, *Nature* 378:203206, 1995 – copies enclosed) that showed that the deletion of Mdm2 in mice causes embryonic lethality owing to the activation of p53. Accordingly, the person of ordinary skill in the art was taught that inhibition of Mdm2 can cause activation of p53 in cells where Mdm2 levels are normal (*i.e.*, not over-expressed) but that this was very deleterious to normal tissue. Accordingly, the person of ordinary skill in the art is strongly taught against considering the inhibition of Mdm2/p53 in cancer cells that expressed Mdm2 at normal levels as a possible therapy. Instead, the findings suggested that such a therapy could well be non-specifically toxic and consequently would not be a good approach for tumors without Mdm2 over-expression.

Instead, the person of ordinary skill in the art would have been aware that some tumors show over-expression of Mdm2 and that it was reasonable to expect that these tumor cells would

be more sensitive to Mdm2 inhibition than normal cells, so the inhibition of Mdm2 could be useful as a cancer therapy specifically in these cases.

It is important to note that it was assumed at that time that in tumors with no over-expression of Mdm2, p53 was inhibited through other, unknown mechanisms. Consequently, it was not known at the time whether inhibition of Mdm2:p53 interaction in such tumors would be an effective therapy, and indeed, there was evidence that such an approach could be very deleterious to normal tissues, which would have advised against even trying this approach.

McCann *et al.* investigate breast cancer cells to determine frequency of over-expression of Mdm2. As mentioned above, they conclude that only 7% of these cancers show over-expressed Mdm2. Thus, McCann *et al.* teach that inactivation of p53 as a consequence of Mdm2 over-expression occurs in only few breast cancers.

The Examiner however believed McCann *et al.* to show that it those cancer cells (*e.g.*, breast cancer cells) which do not over-express Mdm2, the presence of Mdm2 is significantly associated with low level p53. It appears to be on the basis of this belief that the Examiner feels the person of ordinary skill in the art has the motivation to use a peptide inhibitor to treat those cells that do not over-express Mdm2.

It is respectfully submitted that this is an incorrect interpretation of the teaching of McCann *et al.* McCann *et al.* teaches that although most breast cancers do not over-express Mdm2, a few of them do show elevated Mdm2 expression, and these tumors are significantly associated with low (*i.e.*, wild-type) p53 levels. McCann *et al.* state that “*at the protein level, MDM2 tumours were significantly associated with tumours having low levels of p53 staining.*” (Summary, lines 7-8). This means that those few breast cancers that over-express Mdm2 tend to show low levels of p53 – indicating a retention of wild-type p53. It is therefore that the person skilled in the art would, on the basis of the McCann *et al.* disclosure, assume the inhibition of p53:Mdm2 binding to be an effective therapy in only a few (7%) cases of breast cancer, *i.e.*, those cases which showed over-expression of Mdm2.

There is absolutely no teaching in any of the cited art, when taken alone or in any combination, that would entice the person skilled in the art to go against the teaching of the art and modify the teaching of Bottger *et al.* to treat cancer cells having little or no expression of Mdm2.

The Examiner is reminded that the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art, including the general state of the art at the relevant time, suggests the desirability of the combination. As discussed before, not only does the prior art not teach such desirability, it actually provides a strong motivation not to combine the references in the way the Examiner appears to have arrived at the combination underlying the present rejection.

Applicants' position is further supported by the attached Declaration of Professor Karen Vousden, an unquestionable person skilled in the relevant art. The Examiner is respectfully requested to carefully consider the thorough scientific reasoning and evidence provided in the Declaration, which has led Professor Vousden to conclude that the results presented in the instant application are surprising, "given the understanding of the mechanisms involved in p53 function" at the time the present application was filed. (Section 18 of the Declaration).


In view of the foregoing arguments and submitted evidence, the Examiner is respectfully requested to withdraw the present rejection.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early issuance of a Notice of Allowance is respectfully solicited.

Although no fees are believed to be due at this time, please charge any fees, including fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney's Docket No. 39749-0001 APC).

Respectfully submitted,

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